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SCIENTIFIC PAPER

Cost-effectiveness of proton therapy in treating base of skull chordoma

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Abstract

While proton beam therapy (PBT) can offer increased sparing of healthy tissue, it is associated with large capital costs and as such, has limited availability. Furthermore, it has not been well established whether PBT has significant clinical advantages over conventional volumetric modulated arc therapy (VMAT) for all tumour types. PBT can potentially offer improved clinical outcomes for base of skull chordoma (BOSCh) patients compared with photon (X-ray) therapy, however the cost-effectiveness of these treatments is unclear. In this study, the cost-effectiveness of PBT in the treatment of BOSCh patients is assessed, based on an analysis of comparative radiotherapy treatment plans using a radiobiological Markov model. Seven BOSCh patients had treatment plans for the delivery of intensity modulated proton therapy and VMAT retrospectively analysed. The patient outcome (in terms of tumour local control and normal tissue complications) after receiving each treatment was estimated with a radiobiological Markov model. In addition, the model estimated the cost of both the primary treatment and treating any resultant adverse events. The incremental cost-effectiveness ratio (ICER) was obtained for each patient. PBT was found to be cost-effective for 5 patients and cost-saving for 2. The mean ICER was AUD$1,990 per quality adjusted life year gained. Variation of model parameters resulted in the proton treatments remaining cost-effective for these patients. Based on this cohort, PBT is a cost-effective treatment for patients with BOSCh. This supports the inclusion of PBT for BOSCh in the Medicare Services Advisory Committee 1455 application.

Keywords Proton therapy · Cost-effectiveness · Base of skull chordoma · Markov model · Radiobiological models

Introduction

Medicare support for proton beam therapy (PBT) in Australia is currently being considered as part of the Medicare Services Advisory Committee (MSAC) 1455 application. MSAC 1455 considers PBT for a specific list of cancer types and has included a review of clinical evidence for PBT for these cancers. The assessment identified a lack of Level 1 evidence for PBT across multiple tumour types. Due to issues regarding equipoise, funding and availability, there have not been any Phase III randomized clinical trials comparing PBT to conventional photon (X-ray) therapy for the cancer types listed in MSAC 1455. In this case, a lack of evidence does not equate to non-superiority. Therefore, it is important that other approaches are considered when assessing whether new technologies should be supported for funding through the public health system.

Markov models were adopted by the Assessment of New Radiation Oncology Technology and Treatments

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(ANROTAT) project [1], undertaken by the Trans-Tasman Radiation Oncology Group (TROG) and funded by the Australian Federal Government Department of Health and Aging. The group recommends that Markov models be adopted for economic assessments of new health technologies. In the current work, we propose the use of Markov models for assessing the cost-effectiveness of PBT relative to conventional X-ray therapy.

One of the most common indications making use of the Medical Treatment Overseas Program (funded by the Australian Government Department of Health) for PBT is base of skull chordoma (BOSCh). Chordoma is a very rare form of bone tumour, accounting for 1–4% of all primary malignant bone tumours [2] with base of skull cases representing approximately one-third of presentations [3]. Achieving complete surgical removal can be limited by the critical anatomical location. Similarly, postoperative radiotherapy with X-rays can also be limited by the presence of nearby critical organs.

Mailhot Vega et al. [4] have proposed a method of selecting paediatric brain cancer patients to receive PBT based on treatment cost-effectiveness. PBT was found to be cost-effective or even cost-saving, depending on the degree to which the hypothalamus could be spared with protons compared with photons. Peeters et al. [5] have carried out a cost analysis of treating various indications with particle therapies compared with photon therapy, based on construction and operational costs. Treatment costs for various tumour types were sourced through a review of cost-effectiveness studies. Cost differences between particle and photon therapy were found to be larger for BOSCh treatments compared with lung and prostate treatments. The cost-effectiveness of carbon ion therapy in the treatment of BOSCh has been analysed by Jäkel et al. [6], based on studies of local control improvement compared with photon therapy. Primary treatment costs and costs for recurrent tumours were estimated. It was found that if local control exceeds 70% with carbon ion therapy, then the overall treatment costs of carbon ion therapy are lower than that of conventional radiotherapy (assuming a local control rate of 50%). The limitation of their approach is that costs associated with toxicities and productivity losses were not considered. Therefore, it may be possible that carbon ion therapy is cost-effective at a smaller difference in local control. Lundkvist et al. [7] have included the effects of adverse events to evaluate the cost-effectiveness of PBT in the treatment of childhood medulloblastoma. A Markov simulation model was used to combine risks of a wide range of toxicities including hearing loss, intelligence quotient (IQ) loss, hypothyroidism, growth hormone deficiency (GHD), osteoporosis, cardiac disease, and second malignancies. PBT was found to be cost-effective and cost-saving compared with conventional radiation therapy for patients with a high risk of IQ loss or developing GHD. However, in this approach variations in the dosimetry between individual patient treatment plans was not considered directly (population-based risks were applied).

In previous work by our group, a Markov model was developed with the ability to identify patients who would receive the most improved clinical outcome if treated with PBT compared with X-ray therapy [8]. The model predicts the radiobiological effect of a given treatment plan on an individual patient basis. This effect includes contributions from locoregional control, treatment toxicities and radiation-induced malignancies. The inclusion of second radiation-induced cancer risk is particularly important when considering younger patients (who comprise the majority of BOSCh patients) as they have a longer remaining life-time over which to develop second cancers. The output of the Markov model was the quality-adjusted life expectancy (QALE), or the number of quality adjusted life years (QALYs) associated with a radiotherapy treatment plan. This output allows quantitative comparisons of treatment modalities.

In the current work, the previously developed Markov model is extended to include a cost-effectiveness analysis, with the output being the cost of a treatment per QALY gained, also known as the incremental cost-effectiveness ratio (ICER). This work builds on that of Mailhot Vega et al. [4] with the inclusion of second cancer risk, locoregional control and a wider range of potential radiation-induced injuries. The aim of this work was to determine whether BOSCh patients can be treated with PBT cost-effectively, based on individual patient dosimetric analyses.

Methods

Patient cohort and treatment planning

The cohort consisted of 7 female BOSCh patients with a wide range of ages at the time of treatment. The size and characteristics of the cohort was limited by availability as BOSCh is particularly rare. The ages and prescription doses are summarised in Table 1. Each patient had volumetric modulated arc therapy (VMAT) and intensity modulated proton therapy (IMPT) treatment plans generated in the Varian Eclipse 13.7 treatment planning system. VMAT plans consisted of 2 co-planar arcs using a 6 MV Varian TrueBeam HD MLC beam model clinically commissioned at the Royal Adelaide Hospital (RAH). Plans were optimized to a planning target volume (PTV) which was generated from a 3 mm expansion of the CTV. IMPT plans consisted of 2–4 beams with pencil beam weights obtained through robust multi-field optimization (MFO) to the clinical target volume (CTV). Beam range uncertainties of 3% and set-up uncertainties of ± 3 mm were included in the robust optimization.

Table 1 The patient ages at the time of treatment and prescription doses

Patient ID	Age (years)	Treatment schedule (Gy/fraction #)	Comments
1	6	78/39	
2	12	78/39	
3	8	78/39	
4	46	70/35	
5	27	74/37	
6	51	74/37	Pituitary not discernible
7	4	70/35	CT scan did not extent to parotids

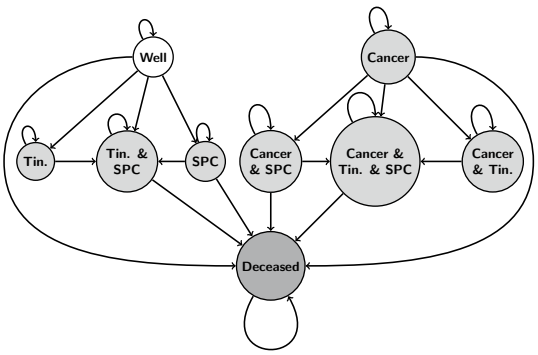

Fig. 1 A simplified Markov state diagram showing allowed transitions between selected states. Only one injury is shown here for clarity, but there is a state for every possible combination of injuries and cancers. Unwell states are represented by pale grey nodes and the Deceased state is represented by a dark grey node. *Cancer* initial primary cancer, *SPC* second primary cancer, *Tin.* tinnitus Adapted from Austin et al. [8]

The proton beam model was based on a Varian ProBeam accelerator.

Markov model

A discrete-time Markov chain model developed previously [8] was extended in this work to model the clinical outcome of each patient. The model consists of several Markov states, with each representing a unique status of health. These include the Well state (or complication-free control), the Deceased state, and the states representing various treatment complications. These are summarised in Fig. 1 and detailed in "Second primary cancers" and "Injuries" sections. In addition, there are states representing an unsuccessful treatment.

It is assumed that a patient occupies a single state at a given time. In each cycle (defined to be 1 year in this work), it is possible for the patient to transition to another state based on certain probabilities. For example, the probability of transitioning from the Well state to an injured state is given by the calculated normal tissue complication probability (NTCP) corresponding to the injury for the patient being considered.

The transition probabilities in the model can be either dose-dependent or dose-independent. The probabilities of locoregional control, second cancer induction and normal tissue complication are dose-dependent and are calculated using the dose-volume histogram (DVH) data from a given treatment plan. Death and recovery probabilities were assumed to be dose-independent in this work.

Locoregional control

The DVH data for the tumour volume for each patient was used to determine a tumour control probability (TCP) that was unique for each patient (details described by Austin et al. [8]). In the event of treatment failure, it is assumed the patients cannot return to the well state (i.e. no retreatments). While this is a simplification of the disease progression, the clinical outcome of the two alternate primary treatments are the subjects of comparison in the model.

The yearly death probability (due to treatment failure), denoted Pr(*Die*), applied in this analysis was 0.4. This was derived from 5-year survival rates after relapse (local or distant) of base of skull chordoma [9] (7%), by evaluating $S = (1 - \Pr(Die))^n$, where $n = 5$ and $S = 0.07$. Solving for the death probability gives 0.4. There is an additional risk of death each year due to unrelated causes. The annual probability of this was derived using Life Tables published by the Australian Bureau of Statistics [10].

Second primary cancers

The volumes used to calculate the time-dependent second primary cancer induction probability (SPCIP) for each patient included the brain and the whole body (with the brain and tumour volumes subtracted). The SPCIP was then calculated for both of these volumes using the parameters determined by Schneider et al. [11]. The yearly SPCIP derived for each volume was combined into a single probability for each year x after treatment as follows:

$$SPCIP(x) = 1 - (1 - SPCIP_{Body}(x))(1 - SPCIP_{Brain}(x)).$$

Treatment of second primary cancer was not considered. The yearly second cancer death probability was assumed to be 0.08, derived from 5-year survival rates of all cancers combined [12].

Injuries

Several injuries were considered in this analysis. These included brainstem necrosis, spinal cord myelitis, tinnitus (damage to the cochlea), blindness (damage in either optic nerve or the optic chiasm), xerostomia (damage to the parotid glands), cataracts (damage to the lens), and endocrine dysfunction (damage to the pituitary gland). The model determined by Lee et al. [13] was used to estimate the NTCP for tinnitus. The model determined by De Marzi et al. [14] was used to estimate the NTCP for endocrine dysfunction. The models used for all other injuries have been described in previous work [8].

It was assumed that all injuries were non-fatal, with the exception of brainstem necrosis, which was assumed to be fatal within 1 year for all patients affected.

All injuries were assumed to be chronic, with the exception of cataracts (which can usually be treated with surgery) and spinal cord myelitis due to a lack of data on long-term costs for this complication.

Estimation of costs and utilities

Costs associated with both the primary radiation treatment and treatment of side effects were incorporated into this model. Each state of health was assigned both a yearly cost and a quality of life utility. By default, the Well state has a utility of 1 and the Deceased state has a utility of 0. All other states have utilities within this interval depending on the impact of the corresponding complication on patient quality of life. The utilities used in this work are listed in Table 2, and are used to calculate the QALE. Second cancers were assumed to have a utility of 0.8. These assumptions are discussed in detail by Austin et al. [8].

No costs were assumed for death, only loss of QALYs. Costs and utilities were discounted by 3% annually, to adjust for differences in timing of costs and effects. In terms of the radiation treatment, the cost of a photon treatment was assumed to be $11,877 [19] and the cost of PBT to be conservatively 2.5 times greater [19]. The costs applied in the model for each injury and the second primary cancer are summarised in Table 3. Re-treatments of cancer are not incorporated into the model and hence the only assumed cost associated with cancers was due to lost productivity. It is likely that the majority of patients in cancer states will move to the Deceased state before they reach the typical retirement age or shortly after in this model. To reduce bias however, the estimated cost of lost productivity was not applied to patients when they were older than 65 years, which is the minimum age to be eligible for the aged pension in Australia. In addition, costs due to lost productivity were not applied when the patient age was less than 18.

Results

The dose-dependent transition probabilities calculated for each plan and for each patient are summarised in Table 4. No patients had a significant risk of brainstem necrosis, spinal cord myelitis, or blindness from any treatment. This is most likely due to these organs being particularly critical and being weighted accordingly during plan optimisation. IMPT was able to provide a much greater probability of locoregional control in some patients (the greatest difference was 0.2 for patient 1). Tinnitus and endocrine dysfunction were the most common injuries in the cohort, although the probabilities of these complications were negligible in some patients, regardless of the treatment. The risk of xerostomia

Table 2 Estimates for the quality of life utilities for states in the Markov model

State	Utility	Comments
Base of skull chordoma	0.72 [15]	
Second primary cancer	0.8	Not clinically founded
Brainstem necrosis	0.6	Not clinically founded
Spinal cord myelitis	0.7 [16]	Utility for spinal cord stenosis taken as an approximation for myelitis
Tinnitus	0.58 [17]	Evaluated after visiting a tinnitus clinic
Blindness	0.33 [16]	Complete blindness
Xerostomia	0.83 [15]	
Cataracts	0.6 [16]	Advanced lens opacity
Endocrine dysfunction	0.73 [18]	Utility of adult females with growth hormone deficiency. Average of values derived from Belgian and Dutch cohorts

Sources are indicated by superscripts

Table 3 Estimates for the costs for states in the Markov model

State	Cost (AUD$)	Comments
Base of skull chordoma	15,960 [20]	Derived from the annual cost of lost productivity [20]. The reduction in Australia's GDP has been found to be $1738 million due to 108,900 cancer patients not participating in the work force, or approximately $15,960 per patient per year
Second primary cancer	15,960 [20]	As above
Brainstem necrosis	N/A	Assumed to be fatal in this model
Spinal cord myelitis	43,764 [21]	Based on a cost of one episode. Therefore, this cost was only applied once, rather than annually
Tinnitus	18,918 [22]	Productivity losses included
Blindness	20,520	Based on the estimate that vision impairment cost $9.85 billion in Australia in 2004, corresponding to 480,000 vision-impaired people [23]. The estimate includes both direct healthcare expenditure and indirect costs such as carer costs, lost earnings and welfare payments
Xerostomia	2,950 [24]	Including oral saline rinses, pilocarpine, dental and nutritionist visits and fluoride gel
Cataracts	760 [25]	Cataracts were assumed to be treatable with surgery involving lens extraction and insertion of an intraocular lens in this work. Therefore, the cost was applied once only
Endocrine dysfunction	5,478 [19]	Based on the cost of the medicine required to treat GHD annually [19]. This cost was only applied to patients aged 18 years and under as treatment is usually not necessary beyond this age. However, it was assumed that it was not possible to recover from this injury

Costs were applied annually, unless otherwise stated. Sources are indicated in square brackets

Table 4 Dose-dependent transition probabilities for each patient

Patient #	Treatment	TCP	Brainstem necrosis	Spinal cord myelitis	Tinnitus	Blindness	Xerostomia	Cataracts	Endocrine dysfunction	SPCIP
1	IMPT	0.88	< 0.01	< 0.01	0.98	0.01	< 0.01	< 0.01	1.00	0.01
	VMAT	0.68	< 0.01	< 0.01	0.98	< 0.01	< 0.01	0.24	1.00	0.02
2	IMPT	0.89	< 0.01	< 0.01	0.01	< 0.01	0.01	< 0.01	< 0.01	0.01
	VMAT	0.82	< 0.01	< 0.01	0.01	< 0.01	0.10	< 0.01	< 0.01	0.02
3	IMPT	0.94	0.02	0.02	0.01	< 0.01	< 0.01	< 0.01	0.82	< 0.01
	VMAT	0.75	< 0.01	< 0.01	0.13	< 0.01	< 0.01	< 0.01	0.25	0.01
4	IMPT	0.86	0.01	< 0.01	0.02	< 0.01	< 0.01	< 0.01	0.39	0.01
	VMAT	0.78	< 0.01	< 0.01	0.04	< 0.01	< 0.01	< 0.01	0.79	0.03
5	IMPT	0.83	0.01	0.01	0.48	< 0.01	< 0.01	< 0.01	0.99	0.02
	VMAT	0.79	< 0.01	< 0.01	0.67	< 0.01	< 0.01	0.02	0.84	0.03
6	IMPT	0.62	< 0.01	< 0.01	0.01	< 0.01	< 0.01	< 0.01	–	< 0.01
	VMAT	0.61	< 0.01	< 0.01	0.03	0.01	< 0.01	0.01	–	0.01
7	IMPT	0.83	< 0.01	< 0.01	0.05	< 0.01	–	< 0.01	0.97	0.01
	VMAT	0.74	< 0.01	< 0.01	0.14	0.01	–	0.01	0.83	0.02

The second primary cancer induction probabilities (SPCIPs) listed represents the probability of a second primary cancer within 25 years after treatment. The normal tissue complication probabilities (NTCPs) represent the time integrated probabilities

TCP tumour control probability

was 10 times greater for patient 2 if treated with VMAT (10% compared with 1%). Patient 1 had a 25% chance of developing cataracts if treated with VMAT compared with a negligible probability (< 1%) if treated with IMPT.

The Markov model took the dose-dependent transition probabilities as input to calculate an ICER for each patient (Table 5). In accordance with NICE guidelines [26], an IMPT treatment was classified as cost-effective if it could be provided at a cost of £20,000–30,000 (AUD$36,000–54,000) per QALY gained or less compared with VMAT. Table 5 demonstrates that all patients could be treated with PBT cost-effectively. The mean ICER was AUD$1990 per QALY gained. Of particular interest were patient 5 and patient 7, who had an improved predicted clinical outcome if treated with IMPT. However, this also corresponded to a lower cost compared with VMAT when complication costs were considered. This is likely a result of the elevated dose received by the ear with VMAT in each case.

Table 5 Predicted life expectancies, costs and ICERs for each patient

Patient ID	Treatment	Raw LE (years)	QALE (QALYs)	Cost ($)	ICER ($/QALY)
1	IMPT	68.4	29.8	564,700	20,170
	VMAT	52.8	23.1	428,640	
2	IMPT	63.8	63.2	36,780	1940
	VMAT	58.7	57.2	25,080	
3	IMPT	71.2	55.3	75,120	180
	VMAT	57.8	51.0	74,340	
4	IMPT	34.1	30.3	40,380	1820
	VMAT	31.3	24.4	29,670	
5	IMPT	47.6	28.5	221,310	− 19,840
	VMAT	45.3	26.0	271,310	
6	IMPT	22.9	22.6	40,300	10,260
	VMAT	22.3	21.7	30,850	
7	IMPT	66.2	47.9	109,670	− 610
	VMAT	57.4	41.9	113,360	

QALE quality adjusted life expectancy, *QALY* quality adjusted life year

One-way sensitivity analyses were conducted to test the sensitivity of the results to estimated model parameters. The results are summarised in Table 6. The ICER data used to calculate the cost-effective percentage of the cohort for each sensitivity scenario is given in Online Resource 1. As the most likely driver of the treatment cost ratio is the PBT cost, this cost was varied in the sensitivity analysis. The fraction of the cohort that could be treated cost-effectively remained stable with all parameter variations.

Table 6 The effect of model parameter variation on the percentage of the cohort that could be treated with IMPT cost-effectively

Scenario	Percentage cost-effective
No parameter variation	100
Decreased proton/photon cost ratio to 1.5	100
Increased proton/photon cost ratio to 3.5	100
Primary cancer state	
Decreased cost to 75%	100
Increased cost to 125%	100
Decreased utility by 0.1	100
Increased utility by 0.1	100
Second primary cancer state	
Decreased cost to 75%	100
Increased cost to 125%	100
Decreased utility by 0.1	100
Increased utility by 0.1	100
Tinnitus state	
Decreased cost to 75%	100
Increased cost to 125%	100
Decreased utility by 0.1	100
Increased utility by 0.1	100
Endocrine dysfunction state	
Decreased cost to 75%	100
Increased cost to 125%	100
Decreased utility by 0.1	100
Increased utility by 0.1	100

The treatment cost ratios were altered by altering the proton treatment cost. This cost is more likely to vary compared with the photon treatment cost

Discussion

For all of the cases presented, it was found that the initial cost of the proton treatment was justifiable if the costs associated with the greater risk of radiation-induced toxicity arising from photon treatments are considered. This was predominantly due to reduced risks of tinnitus and endocrine dysfunction, as well as improved tumour control probabilities associated with the IMPT treatments. It was predicted that the proton treatment for two of the patients was cost-saving, that is, the treatment of both the tumour and treatment side effects were both less expensive and resulted in an improved clinical outcome compared with VMAT.

The results presented here are consistent with those of Mailhot Vega et al. [4], in that PBT has been found to be a cost-effective treatment in cases where critical structures can be spared (typically the pituitary and cochlea in this case). While Peeters et al. [5] found a larger cost difference between proton and photon treatments for BOSCh (AUD$26,070) compared with other indications, here proton treatments were found to be cost-effective for BOSCh patients with a mean cost difference of AUD$1990. The

discrepancy between the results presented here and those of Peeters et al. is possibly due to different healthcare systems, as well as our inclusion of costs associated with additional treatment complications.

This work has limitations that should be considered when interpreting the results. The most important limitation was the input data used for the model. A lack of appropriate data on costs and effects has been identified as a significant cause of bias in studies of cost-effectiveness of proton therapy [27]. The quality of life utilities associated with the endocrine dysfunction state and the BOSCh state were derived from adult populations (the BOSCh utility was also based on a Dutch population) and may not be representative of the quality of life experienced by a paediatric patient, which may influence the ICER calculated for certain patients in the cohort considered here. Furthermore, it is possible that endocrine dysfunction could be associated with costs other than that of treating GHD, and the cost assumed in this work could be underestimated as a result. However, the results were stable with variations in the costs and utilities associated with this injury and with the BOSCh state. The assumed cost of spinal cord myelitis could also be underestimated as it did not include treatment of additional complications associated with the condition. However, the NTCP calculated for this injury was < 0.01 for most patients and did not exceed 0.02 for any patient or treatment, so it is unlikely that this assumption impacted the results. As recommended by Lievens and Pijls-Johannesma [27], the quality of the input parameters could be continuously refined though collection of outcomes data with population-based registries.

No costs were assumed for premature death. Due to the large TCP difference between IMPT and VMAT treatments for many patients, this assumption likely underestimates the costs associated with VMAT. There was also difficulty in sourcing accurate injury development times, resulting in a degree of uncertainty in the costs and QALYs.

Another important limitation of this work was the cohort size utilised. The size of the cohort used in the analysis was limited as BOSCh is a relatively rare disease. A larger cohort would have increased the generalizability of the conclusions drawn from this study.

Model validation is an important step in the process of developing individualised patient selection strategies [28]. The estimated SPCIPs for several patients in the cohort were comparatively low considering observations of second malignancy incidences in all treatment sites. These have been found to be 7.5% for photons and 5.3% for protons (median follow up of 6.7 years) [29]. The model used to calculate the SPCIP in this work is yet to be validated, and this is the likely reason for the discrepancy between this work and the observations.

Conclusion

Markov modelling provides a means for timely assessment of new technologies in radiation oncology. This concept has been applied in the current work on an individual patient dosimetry basis for the assessment of cost-effectiveness of PBT for BOSCh. The model suggested all patients analysed could be treated cost-effectively with PBT when compared to VMAT. Sensitivity analyses demonstrated the robustness of these results. This form of assessment may prove useful in guiding public health system support for patients to receive PBT in Australia.

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Compliance with ethical standards

Conflict of interest Scott Penfold has worked part-time for a developer of a proton therapy centre. The other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Royal Adelaide Hospital Research Ethics Committee No. 150322) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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